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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

PATHEON SOFTGELS INC., BIONPHARMA INC. and BIONPHARMA HEALTHCARE LLC, Plaintiffs, v. APOTEX INC. and APOTEX CORP., Defendants.	Civil Action No.: **COMPLAINT FOR PATENT INFRINGEMENT** *Filed Electronically*

Plaintiffs Patheon Softgels Inc. ("Patheon Softgels"), and Bionpharma Inc. and Bionpharma Healthcare LLC (collectively, "Bionpharma") (Patheon Softgels and Bionpharma are collectively referred to herein as "Plaintiffs"), by their attorneys, for their complaint against Apotex Inc. and Apotex Corp. (collectively, "Apotex") allege as follows:

NATURE OF THE ACTION

1. This is a civil action for infringement of United States Patent Nos. 9,693,978 (the "'978 patent") and 9,693,979 (the "'979 patent") (collectively, the "Patents-in- suit") under the patent laws of the United States, 35 U.S.C. §100, *et seq*. This action arises from Apotex's filing of Abbreviated New Drug Application ("ANDA") No. 210325 ("the Apotex ANDA") with the United States Food and Drug Administration ("FDA") seeking approval to commercially market a generic version of Bionpharma's 220 mg Naproxen Sodium (EQ 200 mg Base) Over-the-Counter ("OTC")

drug product ("the Apotex ANDA Product") prior to the expiration of the Patents-in-suit.

THE PARTIES

2. Patheon Softgels is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 4125 Premier Drive, High Point, North Carolina 27265.

3. Bionpharma Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 600 Alexander Road, Suite 2-4B, Princeton, New Jersey 08540.

4. Bionpharma Healthcare LLC is a Delaware limited liability company, having a principal place of business at 600 Alexander Road, Suite 2-4B, Princeton, New Jersey 08540.

5. Upon information and belief, defendant Apotex Inc. is a foreign corporation organized and existing under the laws of Canada, having a principal place of business at 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9.

6. Upon information and belief, defendant Apotex Corp. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 2400 North Commerce Parkway, Weston, Florida 33326.

THE PATENTS-IN-SUIT

7. On July 4, 2017, the United States Patent and Trademark Office ("USPTO") duly and lawfully issued the '978 patent, entitled "Solvent System for Enhancing the Solubility of Pharmaceutical Agents." Patheon Softgels is the owner and assignee of the '978 patent. A copy of the '978 patent is attached as Exhibit A.

8. Bionpharma has an exclusive license under the '978 patent.

9. On July 4, 2017, the USPTO duly and lawfully issued the '979 patent, entitled "Liquid Dosage Forms of Sodium Naproxen." Patheon Softgels is the owner and assignee of the

'979 patent. A copy of the '979 patent is attached as Exhibit B.

10. Bionpharma has an exclusive license under the '979 patent.

BIONPHARMA'S NDA AND NAPROXEN SODIUM DRUG PRODUCT

11. Bionpharma holds approved New Drug Application ("NDA") No. 021920 for 220 mg Naproxen Sodium (EQ 200 mg Base) OTC capsules ("the Bionpharma NDA Product").

12. Pursuant to 21 U.S.C. § 355(b)(1), and attendant FDA regulations, the '978 and '979 patents are listed in the FDA publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to NDA No. 021920.

13. Bionpharma sells the Bionpharma NDA Product throughout the United States, including in this Judicial District.

14. Patheon Softgels manufactures the Bionpharma NDA Product for Bionpharma.

JURISDICTION AND VENUE

15. This action arises under the patent laws of the United States, 35 U.S.C. §§ 100, *et seq.*, and this Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331, 1338(a), 2201 and 2202.

16. This Court may declare the rights and other legal relations of the parties pursuant to 28 U.S.C. §§ 2201-2202 because this is a case of actual controversy within the Court's jurisdiction.

17. Upon information and belief, Apotex Inc. and Apotex Corp. are agents of each other with respect to formulating, manufacturing, packaging, marketing, and/or selling pharmaceutical products throughout the United States and will do the same with respect to the Apotex ANDA Product.

18. Upon information and belief, Apotex Inc. and Apotex Corp. are acting in concert with each other with respect to formulating, manufacturing, packaging, marketing, and/or selling pharmaceutical products throughout the United States and will do the same with respect to the

Apotex ANDA Product.

19. Upon information and belief, Apotex Inc., alone and/or together with its subsidiary, agent or alter ego Apotex Corp., filed Apotex's ANDA No. 210325 with the FDA.

20. Upon information and belief, Apotex Corp. acts at the direction, and for the benefit, of Apotex Inc., and is controlled and/or dominated by Apotex Inc.

21. This Court has personal jurisdiction over Apotex Inc. because, *inter alia*, upon information and belief: (1) it has purposely availed itself of the privilege of doing business in New Jersey, including directly or indirectly through its subsidiary, agent, and/or alter ego, Apotex Corp., a company registered with the State of New Jersey as a drug wholesaler under Registration No. 5003192; (2) it maintains pervasive, continuous, and systematic contacts with the State of New Jersey, including through the marketing, distribution, and/or sale of generic pharmaceutical drugs (for which it is the holder of the approved FDA application) in New Jersey, including directly or indirectly through its subsidiary, agent, and/or alter ego, Apotex Corp.; (3) Apotex Inc. sent Bionpharma a letter dated November 15, 2017, addressed to Bionpharma in Princeton, New Jersey, where Apotex Inc. states that it is seeking approval to engage in the commercial manufacture, use, sale, and/or importation of the Apotex ANDA Product prior to the expiration of the '978 patent ("the Apotex Notice Letter regarding the '978 patent"), and Apotex Inc. sent Bionpharma a letter dated November 15, 2017, addressed to Bionpharma in Princeton, New Jersey, where Apotex Inc. states that it is seeking approval to engage in the commercial manufacture, use, sale, and/or importation of the Apotex ANDA Product prior to the expiration of the '979 patent ("the Apotex Notice Letter regarding the '979 patent") (collectively, the Apotex Notice Letter regarding the '978 patent and the Apotex Notice Letter regarding the '979 patent are referred to herein as "the Apotex Notice Letters"); (4) when and if Apotex's ANDA No. 210325 is approved, Apotex Inc. and/or

Apotex Corp. intend to and will commit acts of infringement in New Jersey by selling and offering to sell the Apotex ANDA Product throughout the United States, including in New Jersey; and (5) the filing of ANDA No. 210325 by Apotex seeking approval to market the Apotex ANDA Product before the expiration of the Patents-in-Suit has caused, and by the sale of the Apotex ANDA Product by Apotex Inc., Apotex Corp. and/or others before the expiration of the Patents-in-Suit will cause, foreseeable harm to Bionpharma, which is headquartered in New Jersey.

22. Additionally, Apotex Inc. has routinely consented to jurisdiction and/or venue in this Court, and availed itself of the protections afforded by this Court, including by asserting Counterclaims in this Court. *See, e.g.*, *Mitsubishi Tanabe Pharma Corp.et al. v. Apotex, Inc. et al.*, No. 17-5278 (PGS) (DEA) (D.N.J. Dec. 11, 2017); *Celgene Corp. v. Hetero Labs Limited et al.*, No. 17-3387 (ES) (JAD) (D.N.J. Jul. 13, 2017); *Novartis Pharm. Corp. v. Apotex Inc., et al.*, No. 15-3634 (SDW)(LDW) (D.N.J. Aug. 18, 2015); *Astrazeneca AB, et al. v. Apotex Corp., et al.*, No. 15-3379 (FLW)(DEA) (D.N.J. Jul. 20, 2015); *Sanofi-Aventis U.S. LLC, et al. v. Apotex Corp., et al.*, No. 15-287 (MAS)(LHG) (D.N.J. Mar. 20, 2015). Apotex Inc. has further availed itself of the jurisdiction of this Court by previously initiating litigation in this Court. *See, e.g.*, *Apotex Inc. v. Shire LLC*, No. 08-3598 (SRC)(MAS) (D.N.J. Jul. 17, 2008); *Apotex Inc., et al. v. Pharmaceutical Resources, Inc.*, No. 06-1153 (JLL)(MF) (D.N.J. Mar. 10, 2006).

23. Alternatively, to the extent the above facts do not establish personal jurisdiction over Apotex Inc., this Court may exercise jurisdiction over Apotex Inc. pursuant to Federal Rule of Civil Procedure 4(k)(2) because: (a) the claims asserted herein arise under federal law; (b) Apotex Inc. would be a foreign defendant not subject to personal jurisdiction in the courts of any state; and (c) Apotex Inc. has sufficient contacts with the United States as a whole, including, but not limited to, manufacturing and selling generic pharmaceutical products that are distributed throughout the

United States, such that this Court's exercise of jurisdiction over Apotex Inc. satisfies due process.

24. This Court has personal jurisdiction over Apotex Corp. because, *inter alia*, upon information and belief: (1) it has purposely availed itself of the privilege of doing business in New Jersey, including, *inter alia*, securing a New Jersey wholesaler drug distributor's license (Registration No. 5003192); (2) it maintains pervasive, continuous, and systematic contacts with the State of New Jersey, including through the marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey; (3) the Apotex Notice Letters, which were addressed to Bionpharma in Princeton, New Jersey, were each signed by a Mr. Kiran Krishnan, an individual identified in the Apotex Notice Letters as the Senior Vice-President, Global Regulatory Affairs for Apotex Corp., and each of the Apotex Notice Letters further identifies Mr. Krishnan as a U.S. agent authorized to accept service on behalf of Apotex Inc.; (4) when and if ANDA No. 210325 is approved, Apotex Corp. intends to and will commit acts of infringement in New Jersey by selling and offering to sell the Apotex ANDA Product throughout the United States, including in New Jersey; and (5) the filing of ANDA No. 210325 by Apotex seeking approval to market the Apotex ANDA Product before the expiration of the Patents-in-Suit has caused, and by the sale of the Apotex ANDA Product by Apotex Corp. and/or others before the expiration of the Patents-in-Suit will cause, foreseeable harm to Bionpharma, which is headquartered in New Jersey.

25. Additionally, Apotex Corp. has routinely consented to jurisdiction and/or venue in this Court, and availed itself of the protections afforded by this Court, including by asserting Counterclaims in this Court. *See, e.g.*, *Mitsubishi Tanabe Pharma Corp.et al. v. Apotex, Inc. et al.*, No. 17-5278 (PGS) (DEA) (D.N.J. Dec. 11, 2017); *Celgene Corp. v. Hetero Labs Limited et al.*, No. 17-3387 (ES) (JAD) (D.N.J. Jul. 13, 2017); *Novartis Pharm. Corp. v. Apotex Inc., et al.*, No. 15-3634 (SDW)(LDW) (D.N.J. Aug. 18, 2015); *Astrazeneca AB, et al. v. Apotex Corp., et al.*, No.

15-3379 (FLW)(DEA) (D.N.J. Jul. 20, 2015); *Sanofi-Aventis U.S. LLC, et al. v. Apotex Corp., et al.*, No. 15-287 (MAS)(LHG) (D.N.J. Mar. 20, 2015). Apotex Corp. has further availed itself of the jurisdiction of this Court by previously initiating litigation in this Court. *See, e.g., Apotex Inc., et al.v. Pharmaceutical Resources, Inc.*, No. 06-1153 (JLL)(MF) (D.N.J. Mar. 10, 2006).

26. Pursuant to 28 U.S.C. § 1391(c)(3), venue as to Apotex Inc. is proper in this Court because, as set forth above, Apotex Inc. is a foreign corporation and thus does not reside in the United States.

27. Pursuant to 28 U.S.C. §§ 1391 and/or 1400(b), venue as to Apotex Corp. is proper in this Court because, *inter alia*, as set forth above, this Court has personal jurisdiction over Apotex Corp. and Apotex Inc. and thus all defendants reside in New Jersey within the meaning of 28 U.S.C. § 1391, and Apotex Corp. has committed and will commit further acts of infringement in New Jersey, and, upon information and belief, does business in New Jersey through a permanent and continuous presence in the State of New Jersey. For example, Apotex Corp. is registered with the State of New Jersey's Department of Health as a drug manufacturer and wholesaler under Registration No. 5003192 and continuously sells its products in New Jersey. Upon information and belief, Apotex Corp. employs a sales force that includes personnel that regularly and continuously work in New Jersey and, if Apotex Inc. succeeds in obtaining FDA approval of the Apotex ANDA, Apotex Corp. will use its sales force to sell the Apotex ANDA Product in the State of New Jersey.

28. Moreover, neither Apotex Inc. nor Apotex Corp. contested venue in at least 14 actions brought in this Judicial District under the Hatch-Waxman Act, including on several occasions after the Supreme Court's decision in *TC Heartland LLC v. Kraft Foods Grp. Brands LLC*, 137 S.Ct. 1514 (2017). *See, e.g.*, Civ. Action Nos. 17-5399, 17-5278, 17-2423, 15-8492, 15-7880, 15-5909, 15-3634, 15-3379, 15-2384, 15-668, 15-287, 14-8074, 14-4409, and 14-2550.

Moreover, Apotex Inc. and Apotex Corp. admitted that venue is proper in at least two actions brought in this Judicial District under the Hatch-Waxman Act. *See, e.g.*, Civ. Action Nos. 14-1975 and 07-3770.

APOTEX'S INFRINGING ANDA SUBMISSION

29. On or about November 16, 2017, Patheon Softgels received from Apotex's counsel a letter, dated November 15, 2017, stating that Apotex Inc. had submitted the Apotex ANDA to the FDA seeking approval to market the Apotex ANDA Product before the expiration of the '978 patent, and stating that the Apotex ANDA contains a certification pursuant to 21 U.S.C. § 355(j)(2)(vii)(IV) (a "Paragraph IV certification") as to the '978 patent. Bionpharma received the Apotex Letter regarding the '978 patent no earlier than November 16, 2017.

30. On or about November 16, 2017, Patheon Softgels received from Apotex's counsel a letter, dated November 15, 2017, stating that Apotex Inc. had submitted the Apotex ANDA to the FDA seeking approval to market the Apotex ANDA Product before the expiration of the '979 patent, and stating that the Apotex ANDA contains a Paragraph IV certification as to the '979 patent. Bionpharma received the Apotex Letter regarding the '979 patent no earlier than November 16, 2017.

31. Apotex specifically directed the Apotex Notice Letters to Bionpharma's headquarters in Princeton, New Jersey.

32. The Apotex ANDA Product is intended to be a generic version of Bionpharma's 220 mg Naproxen Sodium (EQ 200 mg Base) OTC drug product, which was approved via NDA No. 021920.

33. This action is being commenced before the expiration of 45 days from the date Patheon Softgels and Bionpharma received the Apotex Notice Letters.

COUNT I

Infringement of U.S. Patent No. 9,693,978 by Apotex Under 35 U.S.C. § 271(e)(2)

34. Plaintiffs repeat and reallege paragraphs 1-33 above as if fully set forth herein.

35. By filing its ANDA No. 210325 for the purpose of obtaining approval to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of the Apotex ANDA Product before the expiration of the ’978 patent, Apotex committed an act of infringement under 35 U.S.C. § 271(e)(2).

36. Apotex Inc. has had knowledge of the ’978 patent since at least the date it submitted a Paragraph IV certification to the ’978 patent to FDA in connection with its ANDA No. 210325, which was on or before November 15, 2017, the date that it sent the Apotex Notice Letter regarding the ’978 patent to Patheon Softgels and Bionpharma. Upon information and belief, Apotex Corp. has had knowledge of the ’978 patent since at least November 15, 2017, the date that the Apotex Notice Letter regarding the ’978 patent – which was signed by an officer of Apotex Corp. – was sent to Patheon Softgels and Bionpharma, and Apotex Corp. will have knowledge of the ’978 patent at least upon the date of service of this Complaint.

37. Upon information and belief, the commercial manufacture, use, offer to sell, sale, or importation of the Apotex ANDA product, if approved by the FDA, prior to the expiration of the ’978 patent would infringe the ’978 patent under 35 U.S.C. § 271.

38. Plaintiffs will be substantially and irreparably harmed if Apotex’s infringement of the ’978 patent is not enjoined. Plaintiffs do not have an adequate remedy at law.

39. Plaintiffs are entitled to the relief provided by 35 U.S.C. §271(e)(4), including an order of this Court that the effective date of the approval of the Apotex ANDA be a date that is not earlier than the expiration date of the ’978 patent.

COUNT II

Declaratory Judgment of Infringement of U.S. Patent No. 9,693,978 by Apotex

40. Plaintiffs repeat and reallege paragraphs 1-39 above as if fully set forth herein.

41. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

42. There is an actual case or controversy such that the Court may entertain Plaintiffs' request for declaratory relief consistent with Article III of the United States Constitution, and that actual case or controversy requires a declaration of rights by this Court.

43. Upon information and belief, Apotex has made, and will continue to make, substantial preparation in the United States to manufacture, sell, offer to sell, and/or import the Apotex ANDA Product.

44. The Apotex Notice Letter regarding the '978 patent indicates Apotex's refusal to change the course of its actions directed to obtaining FDA approval for and commercially marketing the Apotex ANDA Product prior to the expiration of the '978 patent.

45. If Apotex commercially makes, uses, offers to sell, or sells the Apotex ANDA Product within the United States, or imports the Apotex ANDA Product into the United States, or induces or contributes to any such conduct during the term of the '978 patent, Apotex would infringe one or more claims of the '978 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

46. Plaintiffs are entitled to a declaratory judgment that the commercial manufacture, use, offer for sale, sale, and/or importation of the Apotex ANDA Product will infringe the '978 patent.

COUNT III

Infringement of U.S. Patent No. 9,693,979 by Apotex Under 35 U.S.C. § 271(e)(2)

47. Plaintiffs repeat and reallege paragraphs 1-46 above as if fully set forth herein.

48. By filing its ANDA No. 210325 for the purpose of obtaining approval to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of the Apotex ANDA Product before the expiration of the '979 patent, Apotex committed an act of infringement under 35 U.S.C. § 271(e)(2).

49. Apotex Inc. has had knowledge of the '979 patent since at least the date it submitted a Paragraph IV certification to the '979 patent to FDA in connection with its ANDA No. 210325, which was on or before November 15, 2017, the date that it sent the Apotex Notice Letter regarding the '979 patent to Patheon Softgels and Bionpharma. Upon information and belief, Apotex Corp. has had knowledge of the '979 patent since at least November 15, 2017, the date that the Apotex Notice Letter regarding the '979 patent – which was signed by an officer of Apotex Corp. – was sent to Patheon Softgels and Bionpharma, and Apotex Corp. will have knowledge of the '979 patent at least upon the date of service of this Complaint.

50. Upon information and belief, the commercial manufacture, use, offer to sell, sale, or importation of the Apotex ANDA product, if approved by the FDA, prior to the expiration of the '979 patent would infringe the '979 patent under 35 U.S.C. § 271.

51. Plaintiffs will be substantially and irreparably harmed if Apotex's infringement of the '979 patent is not enjoined. Plaintiffs do not have an adequate remedy at law.

52. Plaintiffs are entitled to the relief provided by 35 U.S.C. §271(e)(4), including an order of this Court that the effective date of the approval of the Apotex ANDA be a date that is not earlier than the expiration date of the '979 patent.

COUNT IV

Declaratory Judgment of Infringement of U.S. Patent No. 9,693,979 by Apotex

53. Plaintiffs repeat and reallege paragraphs 1-52 above as if fully set forth herein.

54. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

55. There is an actual case or controversy such that the Court may entertain Plaintiffs' request for declaratory relief consistent with Article III of the United States Constitution, and that actual case or controversy requires a declaration of rights by this Court.

56. Upon information and belief, Apotex has made, and will continue to make, substantial preparation in the United States to manufacture, sell, offer to sell, and/or import the Apotex ANDA Product.

57. The Apotex Notice Letter regarding the '979 patent indicates Apotex's refusal to change the course of its actions directed to obtaining FDA approval for and commercially marketing the Apotex ANDA Product prior to the expiration of the '979 patent.

58. If Apotex commercially makes, uses, offers to sell, or sells the Apotex ANDA Product within the United States, or imports the Apotex ANDA Product into the United States, or induces or contributes to any such conduct during the term of the '979 patent, Apotex would infringe one or more claims of the '979 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

59. Plaintiffs are entitled to a declaratory judgment that the commercial manufacture, use, offer for sale, sale, and/or importation of the Apotex ANDA Product will infringe the '979 patent.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A Judgment that Apotex has infringed one or more claims of the ’978 patent by filing ANDA No. 210325;

B. A Declaratory Judgment that Apotex’s making, using, selling, offering to sell, or importing the Apotex ANDA Product before the expiration of the ’978 patent would constitute infringement of one or more claims of the ’978 patent, and/or induce or contribute to infringement of one or more claims of the ’978 patent pursuant to 35 U.S.C. § 271(a), (b) and/or (c);

C. A permanent injunction restraining and enjoining Apotex, and its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of the Apotex ANDA Product until after the expiration of the ’978 patent, or any later expiration of exclusivity to which Plaintiffs are or become entitled;

D. An Order that the effective date of any approval of ANDA No. 210325 relating to the Apotex ANDA Product be a date that is not earlier than the expiration date of the ’978 patent as extended plus any other regulatory exclusivity to which Plaintiffs are or become entitled;

E. A Judgment that Apotex has infringed one or more claims of the ’979 patent by filing ANDA No. 210325;

F. A Declaratory Judgment that Apotex’s making, using, selling, offering to sell, or importing the Apotex ANDA Product before the expiration of the ’979 patent would constitute infringement of one or more claims of the ’979 patent, and/or induce or contribute to

infringement of one or more claims of the ’979 patent pursuant to 35 U.S.C. § 271(a), (b) and/or (c);

G. A permanent injunction restraining and enjoining Apotex and its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of the Apotex ANDA Product until after the expiration of the ’979 patent, or any later expiration of exclusivity to which Plaintiffs are or become entitled;

H. An Order that the effective date of any approval of ANDA No. 210325 relating to the Apotex ANDA Product be a date that is not earlier than the expiration date of the ’979 patent as extended plus any other regulatory exclusivity to which Plaintiffs are or become entitled; and

I. Such other and further relief as the Court may deem just and proper.

Dated: December 29, 2017

By: */s/ Liza M. Walsh*

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CERTIFICATION PURSUANT TO LOCAL CIVIL RULE 11.2

I certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court or of any pending arbitration or administrative proceeding.

Dated: December 29, 2017

By: */s/ Liza M. Walsh*

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CERTIFICATION PURSUANT TO LOCAL CIVIL RULE 201.1

I certify that the above-captioned matter is not subject to compulsory arbitration in that the Plaintiffs seek, *inter alia*, injunctive relief.

Dated: December 29, 2017

By: */s/ Liza M. Walsh*

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EXHIBIT A

US009693978B2

(12) **United States Patent**
Chidambaram et al.

(10) **Patent No.: US 9,693,978 B2**
(45) **Date of Patent: *Jul. 4, 2017**

(54) **SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS**

(71) Applicant: **Banner Life Sciences LLC**, High Point, NC (US)

(72) Inventors: **Nachiappan Chidambaram**, Salt Lake City, UT (US); **Aqeel Fatmi**, Greensboro, NC (US)

(73) Assignee: **Banner Life Sciences LLC**, High Point, NC (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/977,808**

(22) Filed: **Dec. 22, 2015**

(65) **Prior Publication Data**

US 2016/0106841 A1 Apr. 21, 2016

Related U.S. Application Data

(63) Continuation of application No. 11/367,238, filed on Mar. 3, 2006, now abandoned.

(60) Provisional application No. 60/659,679, filed on Mar. 3, 2005.

(51) **Int. Cl.**

A61K 31/192	(2006.01)
A61K 9/48	(2006.01)
A61K 31/765	(2006.01)
A61K 47/12	(2006.01)
A61K 9/50	(2006.01)
A61K 9/00	(2006.01)

(52) **U.S. Cl.**

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(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

Liquid and semi-solid pharmaceutical compositions, which can be administered in liquid form or can be used for preparing capsules, are described herein. The composition comprises the salt of one ore more active agents, polyethylene glycol, 0.2-1.0 mole equivalents of a de-ionizing agent per mole of active agent, and water. The pH of the composition is adjusted within the range of 2.5-7.5. The de-ionizing agent causes partial de-ionization (neutralization) of the salt of the active agent resulting in enhanced bioavailability of salts of weakly acidic, basic or amphoteric active agents as well as lesser amounts of polyethylene glycol (PEG) esters.

38 Claims, No Drawings

SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

CROSS REFERENCE TO RELATED APPLICATIONS

The present application is a continuation of U.S. application Ser. No. 11/367,238, filed Mar. 3, 2006, which is related to and claims priority under 35 U.S.C. §119(e) to U.S. provisional patent application U.S. Ser. No. 60/659,679 entitled "Solvent System for Enhancing the Solubility of Pharmaceutical Agents", filed Mar. 8, 2005. The entire contents of these applications are incorporated herein by reference.

FIELD OF THE INVENTION

This invention is in the field of fill materials encapsulated in soft gelatin capsules.

BACKGROUND OF THE INVENTION

Filled one-piece soft gelatin capsules ("softgels") have been widely used for years to encapsulate consumable materials such as vitamins and pharmaceuticals in a liquid vehicle or carrier. Because softgels have properties which are quite different from two-piece hardshell capsules, softgels are more capable of retaining a liquid fill material.

Not all liquids may be enclosed in a softgel capsule. Liquids containing more than about 20% water by weight are generally not enclosed in softgels, because the water tends to dissolve the gelatin shell. Other solvents such as propylene glycol, glycerin, low molecular weight alcohols, ketones, acids, amines, and esters all tend to degrade or dissolve the gelatin shell to some extent.

Softgels are also somewhat sensitive to pH, and generally require a pH in the encapsulated liquid from about 2.5 to about 7.5. Highly acidic liquids may hydrolyze the gelatin, resulting in leaks, while basic liquids may tan the gelatin, resulting in decreased solubility of the gelatin shell.

Pharmaceutical liquids are usually enclosed in softgels as either viscous solutions or suspensions. Suspensions are pharmaceutically less desirable because they can settle during manufacture, which leads to a less uniform product. In contrast, solutions provide the best liquid form for obtaining optimal "content uniformity" in a batch. Further, solutions typically provide a faster and more uniform absorption of an active agent than do suspensions.

Suitable softgel solutions, however, can be difficult to achieve. One constraint is size. Many pharmaceutical agents require volumes of solvent too large to produce a softgel capsule small enough to be taken by patients. The solvent must also have sufficient solvating power to dissolve a large amount of the pharmaceutical agent to produce a concentrated solution and yet not dissolve, hydrolyze or tan the gelatin shell.

Concentrated solutions of pharmaceutical agents for use in softgel capsules have been described. Most of these systems involve ionizing the free pharmaceutical agent in situ to the corresponding salt. For example, U.S. Pat. No. 5,360,615 to Yu et al. discloses a solvent system for enhancing the solubility of acidic, basic, or amphoteric pharmaceutical agents. The solvent system comprises polyethylene glycol, an ionizing agent, and water. The ionizing agent functions by causing the partial ionization of the free pharmaceutical agent. U.S. Pat. No. 6,383,515, U.S. Patent

Application Publication No. 2002/0187195, and U.S. Patent Application Publication No. 2001/0007668 to Sawyer et al. discloses pharmaceutically acceptable solutions containing a medicament suitable for filling softgel capsules comprising a polymer such as polyethylene glycol and an acid salt of a compound having three or more carbon atoms, such as sodium propionate. The salt helps to ionize the medicament without relying on the use of strong acids or bases. U.S. Pat. No. 6,689,382 to Berthel et al. describes a pharmaceutical formulation suitable for filling softgel capsules comprising (a) a therapeutically effective amount of a non-steroidal anti-inflammatory drug (NSAID); and (b) a solvent system comprising 40% to 60% by weight a polyoxyethylene ether, 15% to 35% by weight of glycerin and 15% to 35% by weight water. In cases where the NSAID has a carboxyl or an acidic functional group, the solvent system also includes hydroxide ions. U.S. Pat. No. 5,505,961 to Shelley et al. describes a method for increasing the solubility of acetaminophen alone or in combination with other pharmaceutically active agents to form a clear solution for encapsulation into a softgel capsule. The method comprises solubilizing acetaminophen in a mixture of propylene glycol, polyethylene glycol, water, polyvinylpyrrolidone and sodium or potassium acetate.

The previously described methods all involve the conversion of the free pharmaceutical agent to the corresponding salt. In cases where the free pharmaceutical agent is acidic, the resulting anion can react with the polyethylene glycol in the fill to produce polyethylene glycol esters, thus reducing the amount of available pharmaceutical agent.

There is a need for a solvent system containing a medicament, which can be encapsulated in a softgel capsule, wherein the formation of PEG esters is minimized.

Therefore it is an object of the invention to provide a stable solvent system for pharmaceutical agents, which is suitable for encapsulation in a softgel capsule, wherein the formation of PEG esters is minimized.

BRIEF SUMMARY OF THE INVENTION

Liquid and semi-solid pharmaceutical compositions, which can be administered in liquid form or can be used for preparing capsules, are described herein. The composition comprises the salt of one or more active agents, and 0.2-1.0 mole equivalents of a de-ionizing agent per mole of active agent. The pH of the composition is adjusted within the range of 2.5-7.5. The de-ionizing agent causes partial de-ionization (neutralization) of the salt of the active agent resulting in enhanced bioavailability of salts of weakly acidic, basic or amphoteric active agents as well as decreased amounts of polyethylene glycol (PEG) esters.

DETAILED DESCRIPTION OF THE INVENTION

I. Composition

A. Fill Materials

1. Drugs to be Formulated

The formulation can contain any therapeutic, diagnostic, prophylactic or nutraceutical agent. Exemplary agents include, but are not limited to, analeptic agents; analgesic agents; anesthetic agents; antiasthmatic agents; antiarthritic agents; anticancer agents; anticholinergic agents; anticonvulsant agents; antidepressant agents; antidiabetic agents; antidiarrheal agents; antiemetic agents; antihelminthic agents; antihistamines; antihyperlipidemic agents; antihypertensive agents; anti-infective agents; anti-inflammatory

agents; antimigraine agents; antineoplastic agents; antiparkinson drugs; antipruritic agents; antipsychotic agents; antipyretic agents; antispasmodic agents; antitubercular agents; antiulcer agents; antiviral agents; anxiolytic agents; appetite suppressants (anorexic agents); attention deficit disorder and attention deficit hyperactivity disorder drugs; cardiovascular agents including calcium channel blockers, antianginal agents, central nervous system ("CNS") agents, beta-blockers and antiarrhythmic agents; central nervous system stimulants; diuretics; genetic materials; hormonolytics; hypnotics; hypoglycemic agents; immunosuppressive agents; muscle relaxants; narcotic antagonists; nicotine; nutritional agents; parasympatholytics; peptide drugs; psychostimulants; sedatives; sialagogues, steroids; smoking cessation agents; sympathomimetics; tranquilizers; vasodilators; beta-agonist; and tocolytic agents.

A first class of drugs is selected based on inclusion in the molecule of a weakly acidic, basic or amphoteric group that can form a salt. Any drug that bears an acidic or a basic functional group, for example, an amine, imine, imidazoyl, guanidine, piperidinyl, pyridinyl, quaternary ammonium, or other basic group, or a carboxylic, phosphoric, phenolic, sulfuric, sulfonic or other acidic group, can react with the de-ionizing agent.

Some specific drugs that bear acidic or basic functional groups and thus may be converted to the corresponding salt for use in the described formulations include, but are not limited to, Acetaminophen, Acetylsalicylic acid, Alendronic acid, Alosetron, Amantadine, Amlopidine, Anagrelide, Argatroban, Atomoxetine, Atrovastatin, Azithromycin dehydrate, Balsalazide, Bromocriptan, Bupropion, Candesartan, Carboplatin, Ceftriaxone, Clavulonic acid, Clindamycin, Cimetadine, Dehydrocholic (acid), Dexmethylphenidate, Diclofenac, Dicyclomine, Diflunisal, Diltiazem, Donepezil, Doxorubicin, Doxepin, Epirubicin, Etodolic acid, Ethacrynic acid, Fenoprofen, Fluoxetine, Flurbiprofen, Furosemide, Gemfibrozil, Hydroxyzine, Ibuprofen, Imipramine, Indomethacin, Ketoprofen, Levothyroxine, Maprolitline, Meclizine, Methadone, Methylphenidate, Minocycline, Mitoxantone, Moxifloxacin, Mycophenolic acid, Naproxen, Niflumic acid, Ofloxacin, Ondansetron, Pantoprazole, Paroxetine, Pergolide, Pramipexole, Phenytoin, Pravastain, Probenecid, Rabeprazole, Risedronic acid, Retinoic acid, Ropinirole, Selegiline, Sulindac, Tamsulosin, Telmisertan, Terbinafine, Theophyline, Tiludronic Acid, Tinzaparin, Ticarcillin, Tometin, Valproic acid, Salicylic acid, Sevelamer, Ziprasidone, Zoledronic acid, Acetophenazine, Albuterol, Almotriptan, Amitriptyline, Amphetamine, Atracurium, Beclomethasone, Benztropine, Biperiden, Bosentan, Bromodiphenhydramine, Brompheniramine carbinoxamine, Caffeine, Capecitabine, Carbergoline, Cetirizine, Chlocylizine, Chlorpheniramine, Chlorphenoxamine, Chlorpromazine, Citalopram, Clavunate potassium, Ciprofloxacin, Clemastine, Clomiphene, Clonidine, Clopidogrel, Codeine, Cyclizine, Cyclobenzaprine, Cyproheptadine, Delavirdine, Diethylpropion, Divalproex, Desipramine, Dexmethylphenidate, Dexbrompheniramine, Dexchlopheniramine, Dexchlor, Dextroamphetamine, Dexedrine, Dextromethorphan, Fiflunisal, Diphemanil methylsulphate, Diphenhydramine, Dolasetron, Doxylamine, Enoxaparin, Ergotamine, Ertepenem, Eprosartan, Escitalopram, Esomeprazole, Fenoldopam, Fentanyl, Fexofenadine, Flufenamic acid, Fluvastatin, Fluphenazine, Fluticasone, Fosinopril, Frovatriptan, Gabapentin, Galatamine, Gatifloxacin, Gemcitabine, Haloperidol, Hyalurondate, Hydrocodone, Hydroxychloroquine, Hyoscyamine, Imatinib, Imipenem, Ipatropin, Lisinopril, Leuprolide, Levopropoxyphene, Losartan, Meclofenamic acid, Mefanamic acid, Mesalamine, Mepenzolate, Meperidine, Mephentermine, Mesalimine, Mesoridazine, Metaproteranol, Metformin, Methdialazine, Methscopolamine, Methysergide, Metoprolol, Metronidazole, Mibefradil, Montelukast, Morphine, Mometasone, Naratriptan, Nelfinavir, Nortriptylene, Noscapine, Nylindrin, Omeprazole, Orphenadrine, Oseltamivir, Oxybutynin, Papaverine, Pentazocine, Phendimetrazine, Phentermine, Pioglitazone, Pilocarpine, Prochloroperazine, Pyrilamine, Quetapine, Ranitidine, Rivastigmine, Rosiglitazone, Salmetrol, Sertaline, Sotalol, Sumatriptan, Tazobactam, Tacrolimus, Tamoxifen, Ticlopidine, Topiramate, Tolterodine, Triptorelin, Triplennamine, Triprolidine, Tramadol, Trovofloxacin, Ursodiol, Promazine, Propoxyphene, Propanolol, Pseudoephedrine, Pyrilamine, Quinidine, Oxybate sodium, Sermorelin, Tacrolimus, Tegaseroid, Teriparatide, Tolterodine, Triptorelin pamoate, Scoplolamine, Venlafaxine, Zamivir, Aminocaproic acid, Aminosalicylic acid, Hydromorphone, Isosuprine, Levorphanol, Melhalan, Nalidixic acid, and Para-aminosalicylic acid.

2. Deionizing Agent

The deionizing agent functions by causing partial deionization (neutralization) of the salt of one or more pharmaceutically active agents. When the active agent is the salt of a weak acid and a strong base, the deionizing agent is preferably a hydrogen ion species. When the active agent is the salt of a weak base and a strong acid, the deionizing agent is preferably a hydroxide ion species. The deionizing agent is preferably present in an amount between 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent.

Exemplary hydrogen ion species useful as de-ionizing agents described herein, include, but are not limited to, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

Exemplary hydroxide ion species useful as de-ionizing agents described herein, include, but are not limited to, metal hydroxides such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, aluminum hydroxide, and magnesium hydroxide.

Additional acid or base can be added to adjust the pH of the fill composition. In a preferred embodiment, the pH of the fill composition is from about 2.5 to about 7.5.

3. Excipients

Formulations may be prepared using a pharmaceutically acceptable carrier composed of materials that are considered safe and effective and may be administered to an individual without causing undesirable biological side effects or unwanted interactions. The carrier is all components present in the pharmaceutical formulation other than the active ingredient or ingredients. As generally used herein "carrier" includes, but is not limited to, plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents and combinations thereof.

In a preferred embodiment, a mixture of polyethylene glycol and water is used as a solvent for the salt of the active agent and the de-ionizing agent. Polyethylene glycol is present in an amount from about 10% to about 80% by weight. Water is present in an amount from about 1% to 18% by weight. The molecular weight of polyethylene glycol is between 300 and 1500. Other suitable solvents include surfactants and copolymers of polyethylene glycol. Option-

ally, glycerin, polyvinyl pyrrolidone (PVP) or propylene glycol (PPG) can be added to enhance the solubility of the drug agent.

B. Shell Composition

1. Gelatin

Gelatin is the product of the partial hydrolysis of collagen. Gelatin is classified as either Type A or Type B gelatin. Type A gelatin is derived from the acid hydrolysis of collagen while Type B gelatin is derived from alkaline hydrolysis of collagen. Traditionally, bovine bones and skins have been used as raw materials for manufacturing Type A and Type B gelatin while porcine skins have been used extensively for manufacturing Type A gelatin. In general acid-processed gelatins form stronger gels than lime-processed gelatins of the same average molecular weight.

2. Other Shell Additives

Other suitable shell additives include plasticizers, opacifiers, colorants, humectants, preservatives, flavorings, and buffering salts and acids.

Plasticizers are chemical agents added to gelatin to make the material softer and more flexible. Suitable plasticizers include glycerin, sorbitol solutions which are mixtures of sorbitol and sorbitan, and other polyhydric alcohols such as propylene glycol and maltitol or combinations thereof.

Opacifiers are used to opacify the capsule shell when the encapsulated active agents are light sensitive. Suitable opacifiers include titanium dioxide, zinc oxide, calcium carbonate and combinations thereof.

Colorants can be used to for marketing and product identification/differentiation purposes. Suitable colorants include synthetic and natural dyes and combinations thereof.

Humectants can be used to suppress the water activity of the softgel. Suitable humectants include glycerin and sorbitol, which are often components of the plasticizer composition. Due to the low water activity of dried, properly stored softgels, the greatest risk from microorganisms comes from molds and yeasts. For this reason, preservatives can be incorporated into the capsule shell. Suitable preservatives include alkyl esters of p-hydroxy benzoic acid such as methyl, ethyl, propyl, butyl and heptyl (collectively known as "parabens") or combinations thereof.

Flavorings can be used to mask unpleasant odors and tastes of fill formulations. Suitable flavorings include synthetic and natural flavorings. The use of flavorings can be problematic due to the presence of aldehydes which can cross-link gelatin. As a result, buffering salts and acids can be used in conjunction with flavorings that contain aldehydes in order to inhibit cross-linking of the gelatin.

II. Method of Making

A. Fill Material

The fill material is prepared by mixing the agent (such as a salt of the drug), the deionizing agent, water, and polyethylene glycol at a temperature of 50° C. to 70° C. The resulting solution is encapsulated using the appropriate gel mass. The pharmaceutical agent is present in an amount from about 10% to about 50% by weight. The deionizing agent is present in an amount from about 0.2 to 1.0 mole per mole of the pharmaceutical agent. Water is present in an amount from about 1% to about 20% by weight and polyethylene glycol is present in amount from about 10% to about 80% by weight. Optionally, propylene glycol and/or polyvinyl pyrrolidone are present in an amount from about 1% to about 10%.

B. Gel Mass

The main ingredients of the softgel capsule shell are gelatin, plasticizer, and purified water. Typical gel formulations contain (w/w) 40-50% gelatin, 20-30% plasticizer, and 30-40% purified water. Most of the water is subsequently lost during capsule drying. The ingredients are combined to form a molten gelatin mass using either a cold melt or a hot melt process. The prepared gel masses are transferred to preheated, temperature-controlled, jacketed holding tanks where the gel mass is aged at 50-60° C. until used for encapsulation.

1. Cold Melt Process

The cold melt process involves mixing gelatin with plasticizer and chilled water and then transferring the mixture to a jacket-heated tank. Typically, gelatin is added to the plasticizer at ambient temperature (18-22° C.). The mixture is cooked (57-95° C.) under vacuum for 15-30 minutes to a homogeneous, deaerated gel mass. Additional shell additives can be added to the gel mass at any point during the gel manufacturing process or they may be incorporated into the finished gel mass using a high torque mixer.

2. Hot Melt Process

The hot melt process involves adding, under mild agitation, the gelatin to a preheated (60-80° C.) mixture of plasticizer and water and stirring the blend until complete melting is achieved. While the hot melt process is faster than the cold melt process, it is less accurately controlled and more susceptible to foaming and dusting.

C. Softgel Capsule

Softgel capsules are typically produced using a rotary die encapsulation process. The gel mass is fed either by gravity or through positive displacement pumping to two heated (48-65° C.) metering devices. The metering devices control the flow of gel into cooled (10-18° C.), rotating casting drums. Ribbons are formed as the cast gel masses set on contact with the surface of the drums.

The ribbons are fed through a series of guide rolls and between injection wedges and the capsule-forming dies. A food-grade lubricant oil is applied onto the ribbons to reduce their tackiness and facilitate their transfer. Suitable lubricants include mineral oil, medium chain triglycerides, and soybean oil. Fill formulations are fed into the encapsulation machine by gravity. In the preferred embodiment, the softgels contain printing on the surface, optionally identifying the encapsulated agent and/or dosage.

III. Method of Use

The softgels may be used to encapsulate a wide range of pharmaceutically active agents, nutritional agents and personal care products. Softgel capsules may be administered orally to a patient to deliver a pharmaceutically active agent.

EXAMPLES

In the following examples, the fill material can be prepared by mixing the salt of one or more pharmaceutically active agents, the deionizing agent, water and polyethylene glycol at a temperature of 50° C. to 70° C. The resulting solution can be encapsulated in a softgel capsule using the appropriate gel mass.

Example 1. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85

-continued

Ingredients	% (by weight)
PEG 400	62.30
Water	7.40

Example 2. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4.75
PVP	1.85
PEG 400	60.50
Water	7.40

Example 3. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4.72
PVP	1.85
PEG 400	63.52
Water	7.40

Example 4. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	31.15
Water	7.40
PEG 600	31.15

Example 5. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4075
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Example 6. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4072
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Example 7. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	27.50
Lactic Acid	5.27
Propylene Glycol	2.00
PEG 400	64.64
Water	0.60

Example 8. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	0.24-0.35M
Propylene glycol	2.00
PEG 600.	q.s.

Example 9. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	61.2
PEG 1000	6.80

Example 10. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00

-continued

Ingredients	% (by weight)
PEG 600	51.00
PEG 1000	17.00

Example 11. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	34.00
PEG 1000	34.00

Example 12. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	17.00
PEG 1000	51.00

It is understood that the disclosed invention is not limited to the particular methodology, protocols, and reagents described as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosed invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are as described. Publications cited herein and the materials for which they are cited are specifically incorporated by reference. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

We claim:

1. A pharmaceutical composition comprising soft gelatin capsule comprising a fill material comprising:

(a) a naproxen salt;

(b) about 5% lactic acid by weight of the fill material; and

(c) polyethylene glycol.

2. The composition of claim **1**, wherein polyethylene glycol comprises about 10% to about 80% by weight of the fill material.

3. The composition of claim **1**, wherein the polyethylene glycol comprises one or more polyethylene glycols comprising molecular weights between 300 and 1500.

4. The composition of claim **1**, further comprising one or more excipients.

5. The composition of claim **4**, wherein the excipients comprise plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, or combinations thereof.

6. The composition of claim **1**, further comprising a solubilizer selected from glycerin, polyvinylpyrrolidone, propylene glycol, or a combination thereof.

7. The composition of claim **6**, wherein the solubilizer is present in amount from about 1% to about 10% by weight of the fill material.

8. A method of making the composition of claim **1**, the method comprising the steps of:

(i) mixing the naproxen salt, lactic acid, and polyethylene glycol at an appropriate temperature to form a fill material; and

(ii) encapsulating the fill material in a soft gelatin capsule.

9. The method of claim **8**, wherein the appropriate temperature is from about 50° C. to about 70° C.

10. A soft gelatin capsule comprising a fill material, the fill material comprising:

(a) a naproxen salt;

(b) about 5% lactic acid by weight of the fill material; and

(c) polyethylene glycol.

11. The capsule of claim **10**, wherein polyethylene glycol comprises about 10% to about 80% by weight of the fill material.

12. The capsule of claim **10**, wherein the polyethylene glycol comprises one or more polyethylene glycols comprising molecular weights between 300 and 1500.

13. The capsule of claim **10**, further comprising one or more excipients.

14. The capsule of claim **13**, wherein the excipients comprise plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, or combinations thereof.

15. The capsule of claim **10**, further comprising a solubilizer selected from glycerin, polyvinylpyrrolidone, propylene glycol or a combination thereof.

16. The capsule of claim **15**, wherein the solubilizer comprises about 1% to about 10% by weight of the fill material.

17. A method of using the capsule of claim **10** comprising administering to a patient in need thereof an effective amount of the capsule.

18. A soft gelatin capsule comprising a fill material comprising:

(a) about 10% to about 80% by weight of the fill material polyethylene glycol having a molecular weight between 300 and 1500;

(b) about 10% to about 50% by weight of the fill material naproxen sodium; and

(c) about 5% of the fill material lactic acid.

19. A method of using the capsule of claim **18** comprising administering to a patient in need thereof an effective amount of the capsule.

20. A pharmaceutical composition prepared by a method comprising preparing a fill material comprising:

mixing together

(a) a naproxen salt;

(b) about 5% by weight of the fill material lactic acid; and

(c) polyethylene glycol having a molecular weight between 300 and 1500.

21. A soft gelatin capsule prepared by a method comprising:

(a) producing a fill material by mixing:

(i) a naproxen salt;

(ii) about 5% by weight of the fill material lactic acid;

(iii) polyethylene glycol having a molecular weight between 300 and 1500; and

(b) encapsulating the mixture in a soft gelatin capsule.

22. The composition of claim **1**, wherein the naproxen salt comprises sodium naproxen.

23. The composition of claim **6**, wherein the solubilizer comprises polyvinylpyrrolidone.

24. The method of claim **8**, wherein the naproxen salt comprises sodium naproxen.

25. A capsule produced by the method of claim **8**.

26. The capsule of claim **10**, wherein the naproxen salt comprises sodium naproxen.

27. The capsule of claim **15**, wherein the solubilizer comprises polyvinylpyrrolidone.

28. The capsule of claim **18**, wherein the fill further comprises a solubilizer.

29. The capsule of claim **28**, wherein the solubilizer comprises about 1% to about 10% by weight of the fill material.

30. The capsule of claim **28**, wherein the solubilizer comprises polyvinylpyrrolidone.

31. The method of claim **20**, wherein the naproxen salt comprises sodium naproxen.

32. The method of claim **20**, wherein the fill material further comprises a solubilizer.

33. The method of claim **32**, wherein the solubilizer comprises about 1% to about 10% by weight of the fill material.

34. The method of claim **32**, wherein the solubilizer comprises polyvinylpyrrolidone.

35. The capsule of claim **21**, wherein the naproxen salt comprises sodium naproxen.

36. The capsule of claim **21**, wherein the fill material further comprises a solubilizer.

37. The capsule of claim **36**, wherein the solubilizer comprises about 1% to about 10% by weight of the fill material.

38. The capsule of claim **36**, wherein the solubilizer comprises polyvinylpyrrolidone.

* * * * *

EXHIBIT B

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(12) **United States Patent**
Chidambaram et al.

(10) **Patent No.: US 9,693,979 B2**
(45) **Date of Patent: *Jul. 4, 2017**

(54) **LIQUID DOSAGE FORMS OF SODIUM NAPROXEN**

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(60) Provisional application No. 60/659,679, filed on Mar. 8, 2005.

(51) **Int. Cl.**

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A61K 47/12	(2006.01)
A61K 9/50	(2006.01)
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(52) **U.S. Cl.**

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(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

Described herein are oral pharmaceutical compositions comprising liquid dosage forms of sodium naproxen in soft gel capsules. In one embodiment, the pharmaceutical composition comprises sodium naproxen, 0.2-1.0 mole equivalents of a de-ionizing agent per mole of naproxen, polyethylene glycol, and one or more solubilizers such as propylene glycol, polyvinyl pyrrolidone or a combination thereof.

19 Claims, No Drawings

LIQUID DOSAGE FORMS OF SODIUM NAPROXEN

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a divisional of U.S. patent application Ser. No. 14/977,808, filed on Dec. 22, 2015, which is continuation of U.S. patent application Ser. No. 11/367,238, filed Mar. 3, 2006, which claims priority under 35 U.S.C. §119(e) to U.S. Provisional Patent Application No. 60/659,679, filed Mar. 8, 2005, each of which are incorporated herein in its entirety by express reference thereto.

TECHNICAL FIELD

This application describes liquid dosage forms of sodium naproxen in soft gelatin capsules.

BACKGROUND

Filled one-piece soft gelatin capsules ("softgels") have been widely used for years to encapsulate consumable materials such as vitamins and pharmaceuticals in a liquid vehicle or carrier. Because softgels have properties which are quite different from two-piece hardshell capsules, softgels are more capable of retaining a liquid fill material.

Not all liquids may be enclosed in a softgel capsule. Liquids containing more than about 20% water by weight are generally not enclosed in softgels, because the water tends to dissolve the gelatin shell. Other solvents such as propylene glycol, glycerin, low molecular weight alcohols, ketones, acids, amines, and esters all tend to degrade or dissolve the gelatin shell to some extent.

Softgels are also somewhat sensitive to pH, and generally require a pH in the encapsulated liquid from about 2.5 to about 7.5. Highly acidic liquids may hydrolyze the gelatin, resulting in leaks, while basic liquids may tan the gelatin, resulting in decreased solubility of the gelatin shell.

Pharmaceutical liquids are usually enclosed in softgels as either viscous solutions or suspensions. Suspensions are pharmaceutically less desirable because they can settle during manufacture, which leads to a less uniform product. In contrast, solutions provide the best liquid form for obtaining optimal "content uniformity" in a batch. Further, solutions typically provide a faster and more uniform absorption of an active agent than do suspensions.

Suitable softgel solutions, however, can be difficult to achieve. One constraint is size. Many pharmaceutical agents require volumes of solvent too large to produce a softgel capsule small enough to be taken by patients. The solvent must also have sufficient solvating power to dissolve a large amount of the pharmaceutical agent to produce a concentrated solution and yet not dissolve, hydrolyze or tan the gelatin shell.

Concentrated solutions of pharmaceutical agents for use in softgel capsules have been described. Most of these systems involve ionizing the free pharmaceutical agent in situ to the corresponding salt. For example, U.S. Pat. No. 5,360,615 to Yu et al. discloses a solvent system for enhancing the solubility of acidic, basic, or amphoteric pharmaceutical agents. The solvent system comprises polyethylene glycol, an ionizing agent, and water. The ionizing agent functions by causing the partial ionization of the free pharmaceutical agent. U.S. Pat. No. 6,383,515, U.S. Patent Application Publication No. 2002/0187195, and U.S. Patent Application Publication No. 2001/0007668 to Sawyer et al.

discloses pharmaceutically acceptable solutions containing a medicament suitable for filling softgel capsules comprising a polymer such as polyethylene glycol and an acid salt of a compound having three or more carbon atoms, such as sodium propionate. The salt helps to ionize the medicament without relying on the use of strong acids or bases. U.S. Pat. No. 6,689,382 to Berthel et al. describes a pharmaceutical formulation suitable for filling softgel capsules comprising (a) a therapeutically effective amount of a non-steroidal anti-inflammatory drug (NSAID); and (b) a solvent system comprising 40% to 60% by weight a polyoxyethylene ether, 15% to 35% by weight of glycerin and 15% to 35% by weight water. In cases where the NSAID has a carboxyl or an acidic functional group, the solvent system also includes hydroxide ions. U.S. Pat. No. 5,505,961 to Shelley et al. describes a method for increasing the solubility of acetaminophen alone or in combination with other pharmaceutically active agents to form a clear solution for encapsulation into a softgel capsule. The method comprises solubilizing acetaminophen in a mixture of propylene glycol, polyethylene glycol, water, polyvinylpyrrolidone and sodium or potassium acetate.

The previously described methods all involve the conversion of the free pharmaceutical agent to the corresponding salt. In cases where the free pharmaceutical agent is acidic, the resulting anion can react with the polyethylene glycol in the fill to produce polyethylene glycol esters, thus reducing the amount of available pharmaceutical agent.

There is a need for a solvent system containing a medicament, which can be encapsulated in a softgel capsule, wherein the formation of PEG esters is minimized.

Therefore, it is an object of the invention to provide a stable solvent system for pharmaceutical agents, which is suitable for encapsulation in a softgel capsule, wherein the formation of PEG esters is minimized.

SUMMARY

Liquid and semi-solid pharmaceutical compositions, which can be administered in liquid form or can be used for preparing capsules, are described herein. The composition comprises the salt of one or more active agents, such as naproxen, and 0.2-1.0 mole equivalents of a de-ionizing agent per mole of active agent. The pH of the composition is adjusted within the range of 2.5-7.5. The de-ionizing agent causes partial de-ionization (neutralization) of the salt of the active agent resulting in enhanced bioavailability of salts of weakly acidic, basic or amphoteric active agents as well as decreased amounts of polyethylene glycol (PEG) esters.

Described herein are oral pharmaceutical compositions comprising liquid dosage forms of sodium naproxen in soft gel capsules. In one embodiment, the pharmaceutical composition comprises sodium naproxen, 0.2-1.0 mole equivalents of a de-ionizing agent per mole of naproxen, polyethylene glycol, and one or more solubilizers such as propylene glycol, polyvinyl pyrrolidone or a combination thereof.

One embodiment described herein is a pharmaceutical composition comprising a soft gel capsule encapsulating a liquid matrix comprising: (a) naproxen sodium; (b) one or more deionizing agents comprising fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of naproxen sodium; (c) one or more polyethylene glycols; and (d) one or more solubilizers comprising polyvinylpyrrolidone, propylene glycol, or a combination thereof. In one aspect described herein, the deionizing agent comprises

citric acid or lactic acid. In another aspect described herein, the deionizing agent comprises lactic acid. In another aspect described herein, the polyethylene glycol comprises from about 10% to about 80% by weight of the composition. In another aspect described herein, the polyethylene glycol comprises one or more polyethylene glycols with a molecular weight between 300 and 1500. In another aspect described herein, the polyethylene glycol comprises polyethylene glycol 600. In another aspect described herein, the solubilizer comprises from about 1% to 10% by weight of the composition. In another aspect described herein, the solubilizer comprises about 2% polyvinylpyrrolidone and about 2% propylene glycol. In another aspect described herein, the composition further comprises one or more excipients comprising plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, surfactants, or combinations thereof.

Another embodiment described herein is a pharmaceutical composition comprising: (a) about 25% naproxen sodium by weight; (b) lactic acid in an amount of from about 0.2 to about 1.0 mole equivalents per mole of naproxen sodium; (c) about 10% to about 80% of one or more polyethylene glycols by weight; and (d) about 1% to about 10% by weight of one or more solubilizers comprising polyvinylpyrrolidone, propylene glycol, or a combination thereof. In one aspect described herein, the polyethylene glycol comprises one or more polyethylene glycols with a molecular weight between 300 and 1500. In another aspect described herein, the polyethylene glycol comprises polyethylene glycol 600. In another aspect described herein, the solubilizer comprises propylene glycol and polyvinyl pyrrolidone. In another aspect described herein, the lactic acid comprises about 0.6 mole equivalents per mole of naproxen sodium. In another aspect described herein, the weight percentage of lactic acid is about 5%. In another aspect described herein, the solubilizer comprises about 2% polyvinylpyrrolidone and about 2% propylene glycol. In another aspect described herein, the composition further comprises one or more excipients selected from plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, bioavailability enhancers, solvents, dyes, preservatives, surfactants, or combinations thereof. In another aspect described herein, the pH is from about 2.5 to about 7.5. In another aspect described herein, the composition is encapsulated in a softgel capsule. In another aspect described herein, the softgel capsule comprises: (a) gelatin; (b) plasticizer; and (c) purified water.

Another embodiment described herein is a method for making a pharmaceutical composition, the method comprising: (a) mixing together (i) about 25% naproxen sodium by weight; (ii) lactic acid in an amount of from about 0.2 to about 1.0 mole equivalents per mole of naproxen sodium; (ii) about 10% to about 80% of one or more polyethylene glycols by weight; and (iv) about 1% to about 10% by weight of one or more solubilizers comprising polyvinylpyrrolidone, propylene glycol, or a combination thereof; and (b) encapsulating the mixture in a softgel capsule using rotary die encapsulation.

Another embodiment described herein is an oral dosage form produced by the method described herein.

DETAILED DESCRIPTION

I. Composition
   A. Fill Materials
   1. Drugs to be Formulated

The formulation can contain any therapeutic, diagnostic, prophylactic or nutraceutical agent. Exemplary agents include, but are not limited to, analeptic agents; analgesic agents; anesthetic agents; antiasthmatic agents; antiarthritic agents; anticancer agents; anticholinergic agents; anticonvulsant agents; antidepressant agents; antidiabetic agents; antidiarrheal agents; antiemetic agents; antihelminthic agents; antihistamines; antihyperlipidemic agents; antihypertensive agents; anti-infective agents; anti-inflammatory agents; antimigraine agents; antineoplastic agents; antiparkinson drugs; antipruritic agents; antipsychotic agents; antipyretic agents; antispasmodic agents; antitubercular agents; antiulcer agents; antiviral agents; anxiolytic agents; appetite suppressants (anorexic agents); attention deficit disorder and attention deficit hyperactivity disorder drugs; cardiovascular agents including calcium channel blockers, antianginal agents, central nervous system ("CNS") agents, beta-blockers and antiarrhythmic agents; central nervous system stimulants; diuretics; genetic materials; hormonolytics; hypnotics; hypoglycemic agents; immunosuppressive agents; muscle relaxants; narcotic antagonists; nicotine; nutritional agents; parasympatholytics; peptide drugs; psychostimulants; sedatives; sialagogues, steroids; smoking cessation agents; sympathomimetics; tranquilizers; vasodilators; beta-agonist; and tocolytic agents.

A first class of drugs is selected based on inclusion in the molecule of a weakly acidic, basic or amphoteric group that can form a salt. Any drug that bears an acidic or a basic functional group, for example, an amine, imine, imidazoyl, guanidine, piperidinyl, pyridinyl, quaternary ammonium, or other basic group, or a carboxylic, phosphoric, phenolic, sulfuric, sulfonic or other acidic group, can react with the de-ionizing agent.

Some specific drugs that bear acidic or basic functional groups and thus may be converted to the corresponding salt for use in the described formulations include, but are not limited to, Acetaminophen, Acetylsalicylic acid, Alendronic acid, Alosetron, Amantadine, Amlopidine, Anagrelide, Argatroban, Atomoxetine, Atrovastatin, Azithromycin dehydrate, Balsalazide, Bromocriptan, Bupropion, Candesartan, Carboplatin, Ceftriaxone, Clavulonic acid, Clindamycin, Cimetadine, Dehydrocholic (acid), Dexmethylphenidate, Diclofenac, Dicyclomine, Diflunisal, Diltiazem, Donepezil, Doxorubicin, Doxepin, Epirubicin, Etodolic acid, Ethacrynic acid, Fenoprofen, Fluoxetine, Flurbiprofen, Furosemide, Gemfibrozil, Hydroxyzine, Ibuprofen, Imipramine, Indomethacin, Ketoprofen, Levothyroxine, Maprolitline, Meclizine, Methadone, Methylphenidate, Minocycline, Mitoxantone, Moxifloxacin, Mycophenolic acid, Naproxen, Niflumic acid, Ofloxacin, Ondansetron, Pantoprazole, Paroxetine, Pergolide, Pramipexole, Phenytoin, Pravastain, Probenecid, Rabeprazole, Risedronic acid, Retinoic acid, Ropinirole, Selegiline, Sulindac, Tamsulosin, Telmisertan, Terbinafine, Theophyline, Tiludronic Acid, Tinzaparin, Ticarcillin, Tometin, Valproic acid, Salicylic acid, Sevelamer, Ziprasidone, Zoledronic acid, Acetophenazine, Albuterol, Almotriptan, Amitriptyline, Amphetamine, Atracurium, Beclomethasone, Benztropine, Biperiden, Bosentan, Bromodiphenhydramine, Brompheniramine carbinoxamine, Caffeine, Capecitabine, Carbergoline, Cetirizine, Chlocylizine, Chlorpheniramine, Chlorphenoxamine, Chlorpromazine, Citalopram, Clavunate potassium, Ciprofloxacin, Clemastine, Clomiphene, Clonidine, Clopidogrel, Codeine, Cyclizine, Cyclobenzaprine, Cyproheptadine, Delavirdine, Diethylpropion, Divalproex, Desipramine, Dexmethylphenidate, Dexbrompheniramine, Dexchlopheniramine, Dexchlor, Dextroamphetamine, Dexedrine, Dex-

tromethorphan, Fiflunisal, Diphemanil methylsulphate, Diphenhydramine, Dolasetron, Doxylamine, Enoxaparin, Ergotamine, Ertepenem, Eprosartan, Escitalopram, Esomeprazole, Fenoldopam, Fentanyl, Fexofenadine, Flufenamic acid, Fluvastatin, Fluphenazine, Fluticasone, Fosinopril, Frovatriptan, Gabapentin, Galatamine, Gatifloxacin, Gemcitabine, Haloperidol, Hyalurondate, Hydrocodone, Hydroxychloroquine, Hyoscyamine, Imatinib, Imipenem, Ipatropin, Lisinopril, Leuprolide, Levopropoxyphene, Losartan, Meclofenamic acid, Mefanamic acid, Mesalamine, Mepenzolate, Meperidine, Mephentermine, Mesalimine, Mesoridazine, Metaproteranol, Metformin, Methdialazine, Methscopolamine, Methysergide, Metoprolol, Metronidazole, Mibefradil, Montelukast, Morphine, Mometasone, Naratriptan, Nelfinavir, Nortriptylene, Noscapine, Nylindrin, Omeprazole, Orphenadrine, Oseltamivir, Oxybutynin, Papaverine, Pentazocine, Phendimetrazine, Phentermine, Pioglitazone, Pilocarpine, Prochloroperazine, Pyrilamine, Quetapine, Ranitidine, Rivastigmine, Rosiglitazone, Salmetrol, Sertaline, Sotalol, Sumatriptan, Tazobactam, Tacrolimus, Tamoxifen, Ticlopidine, Topiramate, Tolterodine, Triptorelin, Triplennamine, Triprolidine, Tramadol, Trovofloxacin, Ursodiol, Promazine, Propoxyphene, Propanolol, Pseudoephedrine, Pyrilamine, Quinidine, Oxybate sodium, Sermorelin, Tacrolimus, Tegaseroid, Teriparatide, Tolterodine, Triptorelin pamoate, Scoplolamine, Venlafaxine, Zamivir, Aminocaproic acid, Aminosalicylic acid, Hydromorphone, Isosuprine, Levorphanol, Melhalan, Nalidixic acid, and Para-aminosalicylic acid.

2. Deionizing Agent

The deionizing agent functions by causing partial deionization (neutralization) of the salt of one or more pharmaceutically active agents. When the active agent is the salt of a weak acid and a strong base, the deionizing agent is preferably a hydrogen ion species. When the active agent is the salt of a weak base and a strong acid, the deionizing agent is preferably a hydroxide ion species. The deionizing agent is preferably present in an amount between 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent.

Exemplary hydrogen ion species useful as de-ionizing agents described herein, include, but are not limited to, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

Exemplary hydroxide ion species useful as de-ionizing agents described herein, include, but are not limited to, metal hydroxides such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, aluminum hydroxide, and magnesium hydroxide.

Additional acid or base can be added to adjust the pH of the fill composition. In a preferred embodiment, the pH of the fill composition is from about 2.5 to about 7.5.

3. Excipients

Formulations may be prepared using a pharmaceutically acceptable carrier composed of materials that are considered safe and effective and may be administered to an individual without causing undesirable biological side effects or unwanted interactions. The carrier is all components present in the pharmaceutical formulation other than the active ingredient or ingredients. As generally used herein "carrier" includes, but is not limited to, plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents and combinations thereof.

In a preferred embodiment, a mixture of polyethylene glycol and water is used as a solvent for the salt of the active agent and the de-ionizing agent. Polyethylene glycol is present in an amount from about 10% to about 80% by weight. Water is present in an amount from about 1% to 18% by weight. The molecular weight of polyethylene glycol is between 300 and 1500. Other suitable solvents include surfactants and copolymers of polyethylene glycol. Optionally, glycerin, polyvinyl pyrrolidone (PVP) or propylene glycol (PPG) can be added to enhance the solubility of the drug agent.

B. Shell Compositions

1. Gelatin

Gelatin is the product of the partial hydrolysis of collagen. Gelatin is classified as either Type A or Type B gelatin. Type A gelatin is derived from the acid hydrolysis of collagen while Type B gelatin is derived from alkaline hydrolysis of collagen. Traditionally, bovine bones and skins have been used as raw materials for manufacturing Type A and Type B gelatin while porcine skins have been used extensively for manufacturing Type A gelatin. In general acid-processed gelatins form stronger gels than lime-processed gelatins of the same average molecular weight.

2. Other Shell Additives

Other suitable shell additives include plasticizers, opacifiers, colorants, humectants, preservatives, flavorings, and buffering salts and acids.

Plasticizers are chemical agents added to gelatin to make the material softer and more flexible. Suitable plasticizers include glycerin, sorbitol solutions which are mixtures of sorbitol and sorbitan, and other polyhydric alcohols such as propylene glycol and maltitol or combinations thereof.

Opacifiers are used to opacify the capsule shell when the encapsulated active agents are light sensitive. Suitable opacifiers include titanium dioxide, zinc oxide, calcium carbonate and combinations thereof.

Colorants can be used to for marketing and product identification/differentiation purposes. Suitable colorants include synthetic and natural dyes and combinations thereof.

Humectants can be used to suppress the water activity of the softgel. Suitable humectants include glycerin and sorbitol, which are often components of the plasticizer composition. Due to the low water activity of dried, properly stored softgels, the greatest risk from microorganisms comes from molds and yeasts. For this reason, preservatives can be incorporated into the capsule shell. Suitable preservatives include alkyl esters of p-hydroxy benzoic acid such as methyl, ethyl, propyl, butyl and heptyl (collectively known as "parabens") or combinations thereof.

Flavorings can be used to mask unpleasant odors and tastes of fill formulations. Suitable flavorings include synthetic and natural flavorings. The use of flavorings can be problematic due to the presence of aldehydes which can cross-link gelatin. As a result, buffering salts and acids can be used in conjunction with flavorings that contain aldehydes in order to inhibit cross-linking of the gelatin.

II. Methods of Making

A. Fill Material

The fill material is prepared by mixing the agent (such as a salt of the drug), the deionizing agent, water, and polyethylene glycol at a temperature of 50° C. to 70° C. The resulting solution is encapsulated using the appropriate gel mass. The pharmaceutical agent is present in an amount from about 10% to about 50% by weight. The deionizing agent is present in an amount from about 0.2 to 1.0 mole per mole of the pharmaceutical agent. Water is present in an amount from about 1% to about 20% by weight and poly-

ethylene glycol is present in amount from about 10% to about 80% by weight. Optionally, propylene glycol and/or polyvinyl pyrrolidone are present in an amount from about 1% to about 10%.

B. Gel Mass

The main ingredients of the softgel capsule shell are gelatin, plasticizer, and purified water. Typical gel formulations contain (w/w) 40-50% gelatin, 20-30% plasticizer, and 30-40% purified water. Most of the water is subsequently lost during capsule drying. The ingredients are combined to form a molten gelatin mass using either a cold melt or a hot melt process. The prepared gel masses are transferred to preheated, temperature-controlled, jacketed holding tanks where the gel mass is aged at 50-60° C. until used for encapsulation.

1. Cold Melt Process

The cold melt process involves mixing gelatin with plasticizer and chilled water and then transferring the mixture to a jacket-heated tank. Typically, gelatin is added to the plasticizer at ambient temperature (18-22° C.). The mixture is cooked (57-95° C.) under vacuum for 15-30 minutes to a homogeneous, deaerated gel mass. Additional shell additives can be added to the gel mass at any point during the gel manufacturing process or they may be incorporated into the finished gel mass using a high torque mixer.

2. Hot Melt Process

The hot melt process involves adding, under mild agitation, the gelatin to a preheated (60-80° C.) mixture of plasticizer and water and stirring the blend until complete melting is achieved. While the hot melt process is faster than the cold melt process, it is less accurately controlled and more susceptible to foaming and dusting.

C. Softgel Capsule

Softgel capsules are typically produced using a rotary die encapsulation process. The gel mass is fed either by gravity or through positive displacement pumping to two heated (48-65° C.) metering devices. The metering devices control the flow of gel into cooled (10-18° C.), rotating casting drums. Ribbons are formed as the cast gel masses set on contact with the surface of the drums.

The ribbons are fed through a series of guide rolls and between injection wedges and the capsule-forming dies. A food-grade lubricant oil is applied onto the ribbons to reduce their tackiness and facilitate their transfer. Suitable lubricants include mineral oil, medium chain triglycerides, and soybean oil. Fill formulations are fed into the encapsulation machine by gravity. In the preferred embodiment, the softgels contain printing on the surface, optionally identifying the encapsulated agent and/or dosage.

III. Methods of Use

The softgels may be used to encapsulate a wide range of pharmaceutically active agents, nutritional agents and personal care products. Softgel capsules may be administered orally to a patient to deliver a pharmaceutically active agent.

It is understood that the disclosed invention is not limited to the particular methodology, protocols, and reagents described as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosed invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are as described. Publications cited herein and the materials for which they are cited are specifically incorporated by reference. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

EXAMPLES

In the following examples, the fill material can be prepared by mixing the salt of one or more pharmaceutically active agents, the deionizing agent, water and polyethylene glycol at a temperature of 50° C. to 70° C. The resulting solution can be encapsulated in a softgel capsule using the appropriate gel mass.

Example 1. Naproxen Sodium with Acetic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	62.30
Water	7.40
TOTAL	100%

Example 2. Naproxen Sodium with Citric Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4.75
PVP	1.85
PEG 400	60.50
Water	7.40
TOTAL	100%

Example 3 Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4.72
PVP	1.85
PEG 400	63.52
Water	7.40
TOTAL	100%

Example 4. Naproxen Sodium with Acetic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	31.15
Water	7.40
PEG 600	31.15

-continued

Example 4. Naproxen Sodium with Acetic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
TOTAL	100%

Example 5. Naproxen Sodium with Citric Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	40.75
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25
TOTAL	100%

Example 6. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	40.72
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25
TOTAL	100%

Example 7. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	27.50
Lactic Acid	5.27
Propylene Glycol	2.00
PEG 400	64.64
Water	0.60
TOTAL	100%

Example 8. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	0.24-0.35M
Propylene Glycol	2.00
PEG 600	q.s.
TOTAL	100%

Example 9. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene Glycol	2.00
PEG 600	61.20
PEG 1000	6.80
TOTAL	100%

Example 10. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene Glycol	2.00
PEG 600	51.00
PEG 1000	17.00
TOTAL	100%

Example 11. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene Glycol	2.00
PEG 600	34.00
PEG 1000	34.00
TOTAL	100%

Example 12. Naproxen Sodium with Lactic Acid as the Deionizing Agent Fill Material

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene Glycol	2.00
PEG 600	17.00
PEG 1000	51.00
TOTAL	100%

The invention claimed is:

1. A pharmaceutical composition comprising a soft gelatin capsule encapsulating a liquid matrix comprising:

(a) naproxen sodium;

(b) about 5% lactic acid by weight of the matrix;

(c) one or more polyethylene glycols; and

(d) one or more solubilizers comprising polyvinylpyrrolidone, propylene glycol, or a combination thereof.

2. The composition of claim **1**, wherein the polyethylene glycol comprises from about 10% to about 80% by weight of the matrix.

3. The composition of claim **1**, wherein the polyethylene glycol comprises one or more polyethylene glycols with a molecular weight between 300 and 1500.

4. The composition of claim **1**, wherein the polyethylene glycol comprises polyethylene glycol 600.

5. The composition of claim **1**, wherein the solubilizer comprises from about 1% to 10% by weight of the matrix.

6. The composition of claim **1**, wherein the solubilizer comprises about 2% polyvinylpyrrolidone and about 2% propylene glycol by weight of the matrix.

7. The composition of claim **1**, further comprising one or more excipients comprising plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, bioavailability enhancers, solvents, dyes, preservatives, surfactants, or combinations thereof.

8. A pharmaceutical composition comprising a soft gelatin capsule encapsulating a liquid matrix comprising:

(a) about 25% naproxen sodium by weight of the matrix;

(b) about 5% lactic acid by weight of the matrix;

(c) about 10% to about 80% of polyethylene glycol 600 by weight of the matrix; and

(d) about 1% to about 10% of one or more solubilizers comprising polyvinylpyrrolidone, propylene glycol, or a combination thereof by weight of the matrix.

9. The composition of claim **8**, wherein the solubilizer comprises propylene glycol and polyvinyl pyrrolidone.

10. The composition of claim **8**, wherein the matrix comprises a mole ratio of lactic acid to naproxen sodium of about 0.6.

11. The composition of claim **8**, wherein the solubilizer comprises about 2% polyvinylpyrrolidone and about 2% propylene glycol by weight of the matrix.

12. The composition of claim **8**, wherein the matrix further comprises one or more excipients selected from plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, bioavailability enhancers, solvents, dyes, preservatives, surfactants, or combinations thereof.

13. The composition of claim **8**, wherein the matrix comprises a pH from about 2.5 to about 7.5.

14. The composition of claim **8**, wherein the soft gelatin capsule comprises:

(a) gelatin;

(b) plasticizer; and

(c) purified water.

15. A method for making the pharmaceutical composition of claim **8**, the method comprising:

(a) mixing together the components of **10**(*a*) to **10**(*d*) to form a mixture; and

(b) encapsulating the mixture in a soft gelatin capsule using rotary die encapsulation.

16. An oral dosage form produced by the method of claim **15**.

17. A pharmaceutical composition comprising a soft gelatin capsule encapsulating a liquid matrix comprising:

(a) about 25% naproxen sodium by weight of the matrix;

(b) about 5% lactic acid by weight of the matrix;

(c) quantum sufficit (q.s.) of polyethylene glycol 600; and

(d) about 1% to about 10% of one or more solubilizers comprising polyvinylpyrrolidone, propylene glycol, or a combination thereof by weight of the matrix.

18. The composition of claim **17**, wherein the solubilizer comprises about 2% polyvinylpyrrolidone and about 2% propylene glycol by weight of the matrix.

19. The composition of claim **17**, wherein the matrix comprises a mole ratio of lactic acid to naproxen sodium of about 0.6.

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